METHODS AND COMPOSITIONS FOR TREATING CANCERS AND NEOPLASMS

FIELD

[0001] Described herein are methods of anti-tumor therapy using placental cells.

SUMMARY

[0002] Previous work has established that the act of culturing adherent stromal cells (ASC) under 3D conditions produces ASC with heretofore undescribed properties and characteristics. Described herein are methods of using ASC for treatment, prevention, and inhibition of growth of cancers, tumors, and neoplasms.

[0003] In certain embodiments, the described ASC have been prepared by culturing in 2-dimensional (2D) culture, 3-dimensional (3D) culture, or a combination thereof. Non-limiting examples of 2D and 3D culture conditions are provided in the Detailed Description and in the Examples. Alternatively or in addition, the cells have been treated, in some embodiments, with pro-inflammatory cytokines; and/or are a placental cell preparation. In certain embodiments, the placental cell preparation is predominantly fetal cells; predominantly maternal cells; or a mixture of fetal and maternal cells, which is, in more specific embodiments, enriched for fetal cells or enriched for maternal cells. The term "ASC", except where indicated otherwise, may refer, in various embodiments, to adherent stromal cells either before or after incubation with pro-inflammatory cytokines. In still other embodiments, ASC refers to adherent stromal cells that have not been incubated with pro-inflammatory cytokines.

[0004] Alternatively or in addition, the cells are mesenchymal-like ASC, which exhibit a marker pattern similar to mesenchymal stromal cells, but do not differentiate into osteocytes, under conditions where "classical" mesenchymal stem cells (MSC) would differentiate into osteocytes. In other embodiments, the cells exhibit a marker pattern similar to MSC, but do not differentiate into adipocytes, under conditions where MSC would differentiate into adipocytes. In still other embodiments, the cells exhibit a marker pattern similar to MSC, but do not differentiate into either osteocytes or adipocytes, under conditions where mesenchymal stem cells would differentiate into osteocytes or adipocytes, respectively. The MSC used for comparison in these assays are, in some embodiments, MSC that have been harvested from bone marrow (BM) and cultured under 2D conditions. In other embodiments, the MSC used for comparison have been harvested from BM and cultured under 2D conditions, followed by 3D conditions.

[0005] In various embodiments, the described ASC are able to exert the described therapeutic effects, each of which is considered a separate embodiment, with or without the ASC themselves engrafting in the host. For example, the cells may, in various embodiments, be able to exert a therapeutic effect, without themselves surviving for more than 3 days, more than 4 days, more than 5 days, more than 6 days, more than 7 days, more than 8 days, more than 9 days, more than 10 days, or more than 14 days; or the cells survive for more than 3 days, more than 4 days, more than 5 days, more than 6 days, more than 7 days, more than 8 days, more than 9 days, more than 10 days, or more than 14 days.

[0006] Reference herein to "growth" of a population of cells is intended to be synonymous with expansion of a cell population.

[0007] Except where otherwise indicated, all ranges mentioned herein are inclusive.

[0008] Except where otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the embodiments of the invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

[0010] In the drawings:

[0011] FIG. **1** is a diagram of a bioreactor that can be used to prepare the cells.

[0012] FIG. **2** contains plots of expression of stimulatory and co-stimulatory molecules on ASC. Upper left: Expression of CD80. Upper right: Expression of CD86. Lower left. Expression of CD40. Lower right: Expression of HLA-A/B/C. Negative controls were prepared with relevant isotype fluorescence molecules. Dotted, light, and heavy lines indicate marker-expression by placental ASC, BM cells, and mononuclear cells (MNC), respectively.

[0013] FIG. **3** is a graph of a secretion profile of ASC under normoxic or hypoxic conditions.

[0014] FIG. **4**A is a graph depicting secretion, measured by fluorescence, of various factors following incubation of ASC with TNF-a+IFN-g (unfilled bars) or control media (filled bars). B-C are graphs depicting fold-increase of secretion, measured by fluorescence, of GRO, IL-8, MCP-1, and RANTES (B); and IL-6, MCP-3, Angiogenin, Insulin-like Growth Factor Binding Protein-2 (IGFBP-2), Osteopontin, and Osteoprotegerin (C) following incubation of ASC with TNF-a alone, relative to incubation with control media (no cytokines).

[0015] FIGS. **5**A-B are graphs depicting fold-increase relative to control medium (containing no cytokines) in secretion of MCP-1 (A) and GM-CSF (B) in several experiments, as measured by ELISA.

[0016] FIGS. **6**A-B are graphs depicting secretion of various factors by TNF-a+IFN-g (A) or TNF-a alone (B) in the presence or absence of FBS. In (A), gray, white, and black bars indicate TNF-a+IFN-g; TNF-a+IFN-g+FBS; and control (no cytokines or serum), respectively. In (B), gray,